REMARKS

Applicants thank the Examiner for reconsideration of the originally-proposed restriction groups, for combining restriction Groups III and IV, and for including claims 18-20 in Group I. Applicants also thank the Examiner for her rationale (Office Action of 01 August 2001, at page 3).

The elected Group I claims 1-3, 8-10, and 18-20 are pending, while 4-7, 11-17, and 21-26 were withdrawn by the Examiner pursuant to 37 C.F.R. 1.142 § (b), and are herein cancelled by applicants.

Claims 1-3, 8-10, and 18-20 have been responsively amended herein to recite a requirement that the encoded polypeptides must comprise contiguous sequences of SEQ ID NO:1 and 2. Additionally, conforming functional language has been recited "wherein the polypeptide binds to the extracellular domain (ECD) of HER-2 with an affinity binding constant of at least 10^8 M^{-1}." Support for these amendments in the Specification has been cited, and discussed in view of the Examiner's rejections. Additionally, various amendments have been made in response to the Examiner's § 112 (second paragraph) rejections to further clarify the full scope of that which applicants regard as their invention, and to establish proper dependency of claims 9 and 10.

No new matter has been added.

FORMALITIES

Applicants have responsively amended the specification by substitution of clean paragraphs to reflect proper use of trademarks (*see* Appendix A for marked up versions). Applicants appreciate the importance of Examiner's emphasis of this issue.

Applicants have prepared final formal drawings in response to the Draftsperson's comments.

Rejections under 35 U.S.C. § 112 (Second Paragraph)

The Examiner rejected claims 1-3, 8-10, and 18-20 under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner asserts that the recitation of "extracellular domain ECD" in claims 1-3, 8-10, and 18-20 is unclear, and that "extracellular domain (ECD)" would be a welcome improvement (Office Action of 01 August 2001 at page 4-5, para 5.).

Applicants have accordingly amended claims 1, 3, 10, 18 and 20 to clarify the claimed subject matter. Specifically, these claims now recite "extracellular domain (ECD)," in place of "ECD." Support for this amendment is found throughout the specification (*e.g.*, at page 3, line 5).

Applicants respectfully request withdrawal of this basis of the Examiner's rejection.

The Examiner further asserts that the recitation of "10^8" in claims 1-3, 8-10, and 18-20 is relative and unclear because it lacks "units," and that there is no "standard" provided by the specification (Office Action of 7/17/2001 at page 5, para 6.).

Applicants respectfully traverse this basis of rejection, because the applicable units are widely recognized in the art as being M^{-1}, and because there is support for both the degree "standard" and "units" in the specification. Applicants agree, however, that this is a legitimate point of clarification that should be addressed, and have accordingly amended independent claims 1 and 18 to recite "10^8 M^{-1}" in place of just "10^8." Support for this amendment is found in the specification at page 23, lines 29-30, and Figure 5C, which recite and show, respectively, that "the ECDIIIa peptide bound to intact 17-3-1 cells at **nM** concentrations." Thus the degree of binding was/is detectable in the *nanomolar* range (*i.e.*, corresponding to a binding constant equal to or greater than 10^8 M^{-1}). Additionally, the specification is replete with references to 'binding' and 'high-affinity binding' and recites the intent to disclose novel high-affinity *binders* (*e.g.*,: the specification at page 1, line 30; at page 2 , line 26; at page 6, line 24 (in relation to the binding data Figure 5); at page 7, line 9 (in relation to the binding data of Figure 6)). Applicants respectfully point out that "a patent need not teach, and preferably omits, that which is known in the prior art" (MPEP Section 2164.01; *In re* Buchner, 929 F.2d 660, 661, 18 UPPQ2d 1331,1332 (Fed Cir. 1991)). Applicants, nonetheless realize that the Examiner's position on clarification of this apparent ambiguity is well taken.

Applicants respectfully request withdrawal of this basis of rejection, based on applicants' responsive amendments, and because the term "10^8," as used throughout the specification, was clearly intended to reflect a measure of binding affinity, and more specifically an affinity binding constant, widely recognized in the art as having units of M^{-1}.

Finally, the Examiner asserts that the recitation of the trademark/trade name "HERCEPTIN®" in claims 3 and 10 is inappropriate to designate goods, as opposed to the source of such goods.

Applicants have accordingly amended dependent claims 3 and 10 to recite the generic terminology "the 4D5 humanized monoclonal antibody (HERCEPTIN®)" in place of "HERCEPTIN®," as suggested by the Examiner.

In summary, applicants thank the Examiner for the thoughtful analysis and suggestions relating to the above indefiniteness issues, and respectfully request withdrawal of Examiner's § 112 second paragraph rejections with respect to amended claims 1-3, 8-10, and 18-20. No new matter has been added.

Rejections under 35 U.S.C. § 112 (First Paragraph)

Written description

The Examiner rejected claims 8, 9, and 18-20 under 35 U.S.C. § 112, first paragraph, as either lacking adequate written description to "reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

The Examiner asserts the claims encompass a large polypeptide "genus" encoding a polypeptide of variable sizes, but minimally comprising a fragment of SEQ ID NO:1 or 2, whereas the "specification discloses only the structural features of two species, the polypeptides of SEQ ID NO:1 and 2" (Office Action of 01 August 2001, at page 6, para 9.), indicating that applicants were not in "possession of the broadly claimed genus.

Applicants respectfully traverse this written description rejection in view of applicants' following comments and responsive amendments of claims 8, 9, and 18-20. Applicants have also made clarifying amendment to claims 1, 2 and 3 to conform the claimed subject matter.

In addition to the requirement of the presence of the C terminal 79 amino acid residues of SEQ ID NO:2 in each of the encoded polypeptides, claims 1-3, 8-10, and 18-20 have been amended to recite that the encoded 50 to 79 residues of SEQ ID NO:1, and 80-419 residues of SEQ ID NO:2 must be *contiguous*.

Furthermore, the claims have been amended to recite limiting functional language that the encoded "polypeptide binds to the extracellular domain (ECD) of HER-2 with an affinity binding constant of at least 10^8 M^{-1}."

Accordingly, the alleged "broadly claimed genus" has been substantially narrowed to those polypeptides having a minimal *contiguous* 79 amino acid C terminal core sequence (SEQ ID NO:1), and which *retain the binding affinity of the full-length 419 amino acid p68HER-2 molecule.* Applicants respectfully contend that the amended claimed invention was well within applicants' possession at the time of filing.

Specifically, support for these amendments is found throughout the specification. Applicants invention is the first and only disclosure of a naturally occurring p185HER-2 binding protein and antagonist. Applicants have demonstrated and taught the binding properties of the full-length p68HER-2 and of the ECDIIIa sub-fragment (*see* Specification at page 22; Example 9, and Figure 5). In fact, the ECDIIIa sub-fragment tested in Example 9 was expressed from the pET30a vector (Novagen; see Specification at page 17, line 17) and thus represents a sizable *fusion* protein of ECDIIIa, comprising a heterologous amino terminal region of about 50 amino acids having: a poly-histidine tag; a thrombin cleavage site; an S-tag region; and an enterokinase site. Therefore, applicants have not only disclosed a "minimal" contiguous binding region, but have demonstrated its function in the context of much larger polypeptides; namely p68HER-2, and more significantly—a sizable *diverse* fusion protein).

Note that the recitation of "300" in originally submitted claim 8 was an inadvertent error, and has been amended herein to "80." Support for this amendment is found in the Specification at page 3, line 15.

Applicants respectfully request withdrawal of the Examiner's asserted § 112 first paragraph written description rejection with respect to amended claims 8, 9, and 18-20. Applicants have also made conforming amendments to claims 1, 2 and 3. No new subject matter has been added.

Enablement

The Examiner also rejected claims 1-3, 8-10, and 18-20 under § 112 first paragraph as lacking *enablement*. The Examiner asserts, based on the listed *Wands* factors (citing Ex parte Forman), that the specification does not reasonably enable claims that are broadly drawn to isolated polynucleotides encoding polypeptides comprising "about 50-79 or 69-79 amino acids taken from SEQ ID NO:1, or from about 80-419, or 300-419 or about 350-419 amino acids taken from SEQ ID NO:2," where the "claims do not require that these amino acids be contiguous." (Office Action of 01 August 2001 at page 7, 3rd para of 10.).

Applicants respectfully traverse this § 112 first paragraph *enablement* rejection, based on applicants following comments and limiting amendments of claims 1-3, 8-10, and 18-20.

As discussed above, applicants have amended claims 1-3, 8-10, and 18-20 to recite that the encoded residues of SEQ ID NO:1 or 2 must be *contiguous*.

Additionally, the claims have been amended to recite limiting functional language that the encoded "polypeptide binds to the extracellular domain (ECD) of HER-2 with an affinity binding constant of at least 10^8 M^{-1}."

Furthermore, applicants respectfully disagree with the Examiner's assertion that "the specification provides no objective evidence that any other isolated polypeptides would function as ECDIIIa and p68HER-2 do (Office Action of 01 August 2001, at page 7-8, bridging para). Significantly, as discussed above, the ECDIIIa sub-fragment tested in applicants' Example 9 was expressed from the pET30a vector (Novagen; *see* Specification at page 17, line 17) and thus represents a sizable *fusion* protein of ECDIIIa, comprising a heterologous amino terminal region of about 50 amino acids having: a poly-histidine tag; a thrombin cleavage site; an S-tag region; and an enterokinase site. Therefore, applicants have not only disclosed a "minimal" contiguous binding region, but have demonstrated its function in the context of much larger polypeptides; namely p68HER-2, and more significantly—a sizable *diverse* fusion protein).

Applicants thus respectfully contend that functional diverse fusion proteins having binding affinities for the extracellular domain (ECD) of HER-2 comparable to that of p68HER-2, are indeed within the teachings of the present disclosure, and under *In re Fisher* (cited by the Examiner).

Applicants thank the Examiner for the discussion of *In re Fisher*, Bowie et al. (Science, 1990, 247:1306-1310), Burgess et al., *J. Cell. Bio.* 111:2129-2138, 1990), Lazar et al., Mol. Cell.

Biol. 8:1247-1252, 1988), and Bork (Genome Research, 2000, 10:398-400), and recognize the predictability issues associated with *substitutions* within functional coding regions of proteins, and with comparative sequence analysis.

However, applicants' claims 1-3, 8-10, and 18-20 have been amended to recite that the functional encoded residues of SEQ ID NO:1 or 2 must be *contiguous*, and thus not substituted. Amended claims 1-3, 8-10, and 18-20 require that the C-terminal contiguous 50-79, 69-79, 80-419, or 350-419 amino acid region of SEQ ID NO:1 or 2 be present and unsubstituted.

Therefore, applicants respectfully contend that while the predictability issues raised by the Examiner in citing *In re Fisher*, Bowie, Burgess, Lazar and Bork are highly relevant, the issue has been reasonably addressed by applicant's responsive amendments; namely, the requirements of *contiguous* amino acids of SEQ ID NO:1 or 2, and the functional *binding* language, which adequately serve to make the scope of the claimed subject matter commensurate with the instant teachings.

The Examiner also rejected claims 18-20 under § 112 first paragraph as lacking *enablement*, asserting that there is no requirement that the "50-79 or 69-79 amino acids taken from SEQ ID NO:1," or that the "80-419, or 300-419 or about 350-419 amino acids taken from SEQ ID NO:2" be contiguous, and furthermore that the Specification provides "no guidance or objective evidence" that any such encoded polypeptides, including ECDIIIa or p68HER-2, would "bind to a site other than that bound by the HERCEPTIN antibody." Additionally, the Examiner points out that the binding site of the HERCEPTIN antibody is not defined (Office Action of 01 August 2001 at page 11, second and third full paras under 11.).

Applicants respectfully traverse this § 112 first paragraph *enablement* rejection, based on applicants following comments limiting amendments of claims 18-20.

With respect to the basis of rejection of non-contiguous amino acid sequences, applicants have, as discussed above, amended claims 1-3, 8-10, and 18-20 to recite that that the C-terminal 50-79, 69-79, 80-419, or 350-419 amino acid region of SEQ ID NO:1 or 2 be *contiguous*.

With respect to the basis of rejection of lack of knowledge of the nature of the binding site of the HERCEPTIN® humanized monoclonal antibody, applicants assume that Examiner's intention was with respect to claims 3 and 10, which recite a distinction of binding sites, rather than claims 18-20, which do not and which encompass the **novel** *combined* use of anti-HER-2 monoclonal antibodies *regardless* of the precise nature of binding the extracellular domain of HER-2.

In any event, applicants respectfully contend that the specification at page 12, line17-19, recites that "the site of such binding is different and unaffected by the site of binding of a marketed humanized monoclonal antibody (Herceptin®)." Applicants' evidence in this regard is the results of applicants' Example 10 at pages 23-24 of the Specification. Specifically, Example 10 shows that pECDIIIa and p68HER-2 had no effect on tyrosine phosphorylation of p185HER-2. This is in

marked contrast to the art-recognized effects of the HERCEPTIN® humanized monoclonal antibody at the time of filing of the parent application. There is thus a very strong likelihood that the binding site of pECDIIIa and p68HER-2 is, at least in part, distinct from that of HERCEPTIN® humanized monoclonal antibody.

Applicants nonetheless have, in view of the Examiner's comments, amended claims, 3 and 10 to recite that "the polypeptide binds to a site on the extracellular domain (ECD) of HER-2 that is, at least in part, distinct from the site of binding of the 4D5 humanized monoclonal antibody (HERCEPTIN®).

Therefore, applicants respectfully request withdrawal of the Examiners § 112 first paragraph enablement rejection with respect to amended claims 18-20 (and preemptively with respect to claims 3 and 10). No new matter has been added.

The Examiner also rejected claims 18-20 under § 112 first paragraph as lacking *enablement*, asserting that there is no requirement that the "50-79 or 69-79 amino acids taken from SEQ ID NO:1," or that the "80-419, or 300-419 or about 350-419 amino acids taken from SEQ ID NO:2" be contiguous, and furthermore that given the unpredictable nature of *in vivo* therapy, the Specification provides "no guidance or evidence" that any such encoded polypeptides, including ECDIIIa or p68HER-2, would have "anti-tumor activity, or why one of skill in the art would expect such a function to induce anti-tumor activity (Office Action of 01 August 2001 at pages 12-14).

Applicants respectfully traverse this § 112 first paragraph *enablement* rejection, based on applicants following comments and limiting amendments of claims 18-20.

With respect to the basis of rejection of non-contiguous amino acid sequences, as stated above, applicants have amended claims 1-3, 8-10, and 18-20 to recite that that the C-terminal 50-79, 69-79, 80-419, or 350-419 amino acid region of SEQ ID NO:1 or 2 be *contiguous*.

Applicant's respectfully, but vigorously traverse Examiner's alleged lack of support for pharmacuetical compositions comprising the instant inventive polypeptides.

Specifically, the specification, at page 13, lines 5-23, and Figure 7, provide explicit teachings of anti-tumor cell activity in an art-recognized and accepted model system.

Anchorage independent growth of cells in soft agar was used as a predictive model for tumor cytotoxicity. This is an art-recognized and predictive procedure to examine transforming activity and reflects the tumorigenic and oncogenic potential of cells (DiFore et al., *Science* 237:178-182, 1987; Hudziak et al., *Proc. Natl. Acad. Sci. USA* 84:7159-7163, 1987; and Baasner et al., *Oncogene* 13:901-911, 1996).

The effects of p68HER-2 on anchorage independent growth in soft agar was determined using SKOV-3 carcinoma cells and HER-2 transfected 17-3-1 cells, which are both tumorigenic and overexpress p185HER-2. The cells were suspended in media supplemented with fetal calf serum in the presence or absence of p68HER-2 and incubated for 21 days in a humidified incubator.

Anchorage independent growth was quantitated by counting the number of colonies that contained more than 50 cells. Figure 7 shows that in the presence of p68HER-2, anchorage independent growth of both SKOV-3 cells and 17-3-1 cells was inhibited several fold. Accordingly, these data show that p68HER-2 is not just cytostatic, but cytotoxic and possibly apoptotic.

Thus, applicants respectfully contend that the Examiner's statement (Office Action of 01 August 2001, at page 13, bridging para) that "applicant has demonstrated no anti-tumor function of the ECDIIIa or p68HER-2 polypeptides..." is inappropriate, and does not reasonably reflect the nature and extent of applicant's inventive teachings.

It is unreasonable to construe the fact that the ECDIIIa or p68HER-2 polypeptides do not activate p185HER-2, as an indication that they have no anti-tumor activity. In fact, as stated above the sites of binding of the inventive polypeptides is, at least in part, distinct from that of HERCEPTIN®, a molecule that does affect p185HER-2 activation. Consistent with this binding distinction applicant's data (see Specification at page 9, lines 8-23) indicates that the ECDIIIa or p68HER-2 polypeptides act by preventing activation of the HER-2 receptor by blocking receptor dimerization. Thus, the ability to block activation of p185HER-2, rather that the ability to activate it, is the basis of the anti-tumor cell activity described above.

Finally, applicants thank the Examiner for the discussion of Dillman et al., *J. Clin. Onco.* 12:1497-1555, 1997, and Dermer, *Bio/Technology* 12:320, 1994) regarding the predictability of *in vivo* therapy. However, applicants respectfully submit that the applicable standard under the MPEP is a "reasonable correlation" standard, and not that of the FDA, and that applicants teachings as summarized above, sufficiently address the recognized applicable standard.

In summary, applicants have shown clear efficacy in a widely-recognized model system using human tumor cells. Moreover, and significantly, the nature of applicant's invention (strong specific receptor HER-2 receptor binding) effectively insures highly preferential delivery to the proper site of action; namely cells overexpressing HER-2 receptor.

Therefore, applicants respectfully request withdrawal of the Examiner's § 112 first paragraph *enablement* rejection with respect to amended claims 18-20.

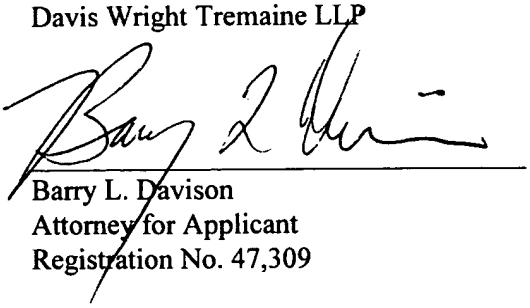
CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully request allowance of the "clean" claim set provided herein above. The Examiner is encouraged to phone applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite allowance of this application.

No new matter has been added. Entry of the Amendment is respectfully requested.

Respectfully submitted,

Davis Wright Tremaine LLP



Barry L. Davison
Attorney for Applicant
Registration No. 47,309

Davis Wright Tremaine LLP
2600 Century Square
1501 Fourth Avenue
Seattle, Washington 98101-1688
Telephone: 206-628-7621
Facsimile: 206-628-7699

Appendix A
(marked-up versions of substitute paragraphs)

(**marked-up version** corresponding to the four (4) contiguous paragraphs beginning on page 2, line 28 and extending through page 3, line 21)

Therefore, there is a need in the art to find molecules that bind to cellular HER-2 and particularly molecules that bind to different sites than humanized antibodies to HER-2 (*e.g.*, [Herceptin®] HERCEPTIN®). Such molecules would be useful therapeutic agents for various cancers that overexpress HER-2.

Summary of the Invention

The present invention provides an isolated polypeptide having from about 50 to 79 amino acids taken from the sequence of SEQ ID NO. 1, wherein the polypeptide binds to the extracellular domain ECD of HER-2 at an affinity of at least 10^8. Preferably, the isolated polypeptide is from about 69 to 79 amino acids in length. Preferably, the isolated polypeptide binds to a site on the ECD of HER-2 that is different from the site of binding of [Herceptin®] HERCEPTIN® (a marketed humanized monoclonal antibody that is used for the treatment of cancer and that binds to the ECD or HER-2).

The present invention further provides an isolated DNA sequence that codes on expression for a polypeptide having from about 50 to 79 amino acids taken from the sequence of SEQ ID NO. 1, wherein the polypeptide binds to the extracellular domain ECD of HER-2 at an affinity of at least 10^8. Preferably, the isolated polypeptide is from about 69 to 79 amino acids in length. Preferably, the isolated polypeptide binds to a site on the ECD of HER-2 that is different from the site of binding of [Herceptin] HERCEPTIN® (a marketed humanized monoclonal antibody that is used for the treatment of cancer and that binds to the ECD or HER-2). The present invention further provides a transfected cell comprising an expression vector having a DNA sequence that codes on expression for a polypeptide having from about 50 to 79 amino acids taken from the sequence of SEQ ID NO. 1, wherein the polypeptide binds to the extracellular domain ECD of HER-2 at an affinity of at least 10^8.

The present invention further provides an isolated and glycosylated polypeptide having from about 80 to 419 amino acids taken from the sequence of SEQ ID NO. 2, wherein the C terminal 79 amino acids are present, and wherein at least three N-linked glycosylation sites are present. Preferably, the isolated polypeptide is from about 350 to 419 amino acids in length and four N-linked glycosylation sites are present. Preferably, the isolated polypeptide binds to a site on the ECD of HER-2 that is different from the site of binding of [Herceptin] HERCEPTIN® (a marketed humanized monoclonal antibody that is used for the treatment of cancer and that binds to the ECD or HER-2).

(**marked-up version** for the paragraph beginning on page 4, line 24 through line 32)

The present invention further provides a method for targeting a therapeutic agent to solid tumor tissue, wherein the solid tumor tissue is characterized by overexpression of HER-2, comprising attaching the therapeutic agent to an isolated polypeptide having from about 50 to 79 amino acids taken from the sequence of SEQ ID NO. 1, wherein the polypeptide binds to the extracellular domain ECD of HER-2 at an affinity of at least 10^8. Preferably, the isolated polypeptide is from about 69 to 79 amino acids in length. Preferably, the isolated polypeptide binds to a site on the ECD of HER-2 that is different from the site of binding of [Herceptin®] HERCEPTIN® (a marketed humanized monoclonal antibody that is used for the treatment of cancer and that binds to the ECD or HER-2).

(**marked-up version** for the paragraph beginning on page 5, line 27 and extending through line 33)

Figure 2 shows the detection of alternative HER-2 transcripts containing the ECDIIIa sequence by Northern blot analysis. PolyA+ mRNA (2.5 μg) from different human fetal tissues (Clontech) or isolated from HEK-293 cells was resolved in a formalin agarose gel and transferred to a [BrightStar®] BRIGHTSTAR® membrane (Ambion) in 10xSSC. The membrane was hybridized with a ^{32}P-labeled antisense RNA probe complimentary to the ECDIII sequence, stripped and reprobed with a ^{32}P labeled cDNA probe specific for the 5' HER-2 exon sequence. The membranes were washed under high stringency conditions and analyzed by phosphorimaging (Molecular Dynamics).

(**marked-up version** for the paragraph beginning on page 12, line 8 and extending through line 20)

The present invention further provides a method for targeting a therapeutic agent to solid tumor tissue, wherein the solid tumor tissue is characterized by overexpression of HER-2, comprising attaching the therapeutic agent to an isolated polypeptide having from about 50 to 79 amino acids taken from the sequence of SEQ ID NO. 1, wherein the polypeptide binds to the extracellular domain ECD of HER-2 at an affinity of at least 10^8. Preferably, the isolated polypeptide is from about 69 to 79 amino acids in length. Preferably, the isolated polypeptide binds to a site on the ECD of HER-2 that is different from the site of binding of [Herceptin®] HERCEPTIN® (a marketed humanized monoclonal antibody that is used for the treatment of cancer and that binds to the ECD or HER-2). It was discovered that the 79 amino acid polypeptide [SEQ ID NO. 1] exhibited surprising high affinity binding properties to the ECD of HER-2. Moreover,

the site of such binding is different and unaffected by the site of binding of a marketed humanized monoclonal antibody ([Herceptin®] HERCEPTIN®). Therefore, the high binding affinity enables the 79 amino acid polypeptide to function as a targeting molecule to tumor cells expressing HER-2.

Appendix B

("marked up" claims, corresponding to those prior pending claims that have been amended herein)

1. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of [having from] about 50 to 79 contiguous residues in length [amino acids taken from the sequence of SEQ ID NO. 1], wherein the polypeptide binds to the extracellular domain (ECD) [ECD] of HER-2 [at] with an affinity binding constant of at least 10^8 M^{-1}.

2. The isolated polypeptide of claim 1, wherein the isolated polypeptide is from about 69 to 79 [amino acids] contiguous residues in length.

3. The isolated polypeptide of claim 1, wherein the isolated polypeptide binds to a site on the extracellular domain (ECD) [ECD] of HER-2 that is, at least in part distinct [different] from the site of binding of the 4D5 humanized monoclonal antibody (HERCEPTIN®) [Herceptin (a marketed humanized monoclonal antibody that is used for the treatment of cancer and that binds to the ECD or HER-2)].

8. An isolated [and glycosylated] polypeptide comprising the amino acid sequence of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of [having from] about 80 [300] to 419 contiguous residues in length [amino acids taken from the sequence of SEQ ID NO. 2], wherein the C terminal 79 contiguous amino acids are present, [and] wherein at least one [three] N-linked glycosylation site [sites] are present, and wherein the polypeptide binds to the extracellular domain (ECD) of HER-2 with an affinity binding constant of at least 10^8 M^{-1}.

9. The isolated [and glycosylated] polypeptide of claim 8 [6], wherein the isolated polypeptide is from about 350 to 419 contiguous residues [amino acids] in length and three [four] N-linked glycosylation are present.

10. The isolated [and glycosylated] polypeptide of claim 8 [6], wherein the isolated polypeptide binds to a site on the extracellular domain (ECD) [ECD] of HER-2 that is, at least in part distinct [different] from the site of binding of the 4D5 humanized monoclonal antibody (HERCEPTIN®) [Herceptin®].

18. A pharmaceutical composition for treating solid tumors that overexpress HER-2, comprising an agent selected from the group consisting of: (a) an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of [having from] about 50 to 79 contiguous residues in length [amino acids taken from the sequence of SEQ ID NO. 1], wherein the polypeptide binds to the extracellular domain (ECD) [ECD] of HER-2 [at] with an affinity binding constant of at least 10^8 M^{-1}; (b) an isolated [and glycosylated] polypeptide comprising the amino acid sequence of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of [having from] about 80 to 419 contiguous residues in length [amino acids taken from the sequence of SEQ ID NO. 2], wherein the C terminal 79 contiguous amino acids are present, [and] wherein at least one [three] N-linked glycosylation site [sites] are present, and wherein the polypeptide binds to the

extracellular domain (ECD) of HER-2 with an affinity binding constant of at least 10^8 M^{-1}; (c) a monoclonal antibody that binds to the extracellular domain(ECD) [ECD] of HER-2; and (d) combinations thereof, with the proviso that the agent cannot be the monoclonal antibody alone, and a pharmaceutically acceptable carrier.

19. The pharmaceutical composition [for treating solid tumors that overexpress HER-2] of claim 18, wherein the agent is the isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of [having from] about 50 to 79 contiguous residues in length [amino acids taken from the sequence of SEQ ID NO. 1].

20. The pharmaceutical composition [for treating solid tumors that overexpress HER-2] of claim 19, wherein the agent is a combination of the isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of [having from] about 50 to 79 contiguous residues in length [amino acids taken from the sequence of SEQ ID NO. 1], and the monoclonal antibody that binds to the extracellular domain (ECD) [ECD] of HER-2.